REMARKS

Formal Matters

Claims 12-14, 16-18, 31 and 33-38 are pending in the application and are amended.

Support for the amendments is found throughout the specification such as, for example, at page 11, line 23 to page 12, line 7; page 15, line 23 to page 16, line 2; page 21, lines 8-18; page 34, lines 3-8; page 36, lines 1-7; page 48, line 1 to page 54, line 18; page 81, line 4 to page 82, line 26; and page 84, lines 3-21. No new matter is added by the amendments.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 16 and 17 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite in that the metes and bounds of "protuberance and cavity" is not clear. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Applicants respectfully disagree that the terms "protuberance and cavity are unclear. Applicants point to disclosures throughout the specification defining and describing the meaning of the terms and how a protuberance and cavity may be generated. Specifically, Applicants point to the specification at, for example, page 11, line 23 to page 12, line 7; page 15, line 23 to page 16, line 2; page 21, lines 8-18; page 34, lines 3-8; page 36, lines 1-7; page 48, line 1 to page 54, line 18; page 81, line 4 to page 82, line 26; and page 84, lines 3-21 for disclosures regarding amino acid side chain protuberance or cavity sufficient to allow one of ordinary skill in the art to practice the invention. As a result, the terms "protuberance and cavity" are not indefinite and the rejection is improper.

Without acquiescing to the rejection and merely to advance prosecution and allowance of the claims, Applicants have amended claims 16 and 17 to describe protuberance and cavity in the

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 12-14, 16-18, 31 and 33-38 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable a multispecific antibody which contains variable light chains having at least 80% amino acid sequence identity. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

The Examiner suggests that the specification, while enabling for bispecific antibodies having identical light chains, does not enable multispecific antibodies because, allegedly, it becomes statistically less probable to isolate antibodies having specificity to multiple antigens and identical light chains. Applicants respectfully point out that many highly successful molecular biology experiments are based on selection and screening processes that greatly enhance obtaining statistically improbable results. Applicants disclose bispecific antibodies having identical light chains which, but for Applicants' disclosure, one might consider improbable. Instead, Applicants have shown that it is possible and have shown a selection process useful for isolation of such bispecific antibodies. Similarly, one of ordinary skill in the art can readily use the guidance of Applicants' specification to isolate multispecific antibodies having identical light chains without undue experimentation. Thus, the claimed invention is enabled by the specification is enabled. The rejection is improper and should be withdrawn.

Without acquiescing to the rejection and merely to expedite prosecution and allowance of the claims, Applicants have amended the claims to recite bispecific antibodies. The rejection is overcome and allowance of the claims is respectfully requested.

In item 6 of the Office Action, the Examiner states that the specification is enabling for the bispecific antibody anti-Ob-R/anti-HER3 where the light chains are identical, but suggest that it is not enabling for multispecific antibodies containing variable light chains with at least 80%

variable light chains. Further, Applicants disclose at Fig. 8 several anti-Ob-R anti-HER3

antibodies screened for antigen binding by panning or ELISA and having at least 80% amino acid sequence identity of the variable light chains (see, also, the specification at page 99, line 5 to page 100, line 10, for example). Applicants have demonstrated the isolation of the many antibodies having different antigen specificity but identical light chains (Table 5), which antibodies can be used to generate bispecific antibodies, as Applicants disclosed. Applicants have further demonstrated, taking the anti-Ob-R/anti-HER3 bispecific antibody as a working example, that the antigen specific portions of the bispecific antibodies include light chains having at least 80% sequence identity, up to 100% sequence identity, as claimed. This disclosure supports the breadth of Applicants' claimed invention because Applicants' specification enables bispecific antibodies with variable light chains having at least 80% sequence identity. Withdrawal of the rejection and allowance of the claims is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 12-14, 16-18, 31 and 33-38 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that Applicants were in possession of the claimed invention. Applicants respectfully traverse the rejection as applied and as it might be applied for the reasons provided below.

The Examiner suggests that Applicants have disclosed only two bispecific antibodies having identical light chains and have disclosed no bispecific antibodies having non-identical light chains. Applicants respectfully point out that the Examiner is mistaken. Applicants disclose in Fig. 8, for example, several bispecific anti-Ob-R/anti-HER3 antibodies having at least 80% amino acid sequence identity of the variable light chain as claimed. Thus, Applicants clearly disclose that they were in possession of the claimed invention at the time the specification

SUMMARY

Claims 12-14, 16-18, 31, and 33-38 are pending in the application. Claim amendments were made merely to expedite prosecution and allowance of the claims. Having overcome the rejections, Applicants respectfully request allowance.

If in the opinion of the Examiner, a **telephone conference** would expedite the prosecution of the subject application, the Examiner is **strongly encouraged** to call the undersigned at the number indicated below.

This response is submitted with a transmittal letter and petition for a three-month extension of time. In the unlikely event that this document is separated from the transmittal letter, Applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,

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Date: August 9, 2002

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 12-14, 16-18, 31, 33-38 are amended as follows, wherein strikeout in brackets [~~00~~] indicates deleted terminology and underling, 00, indicates added terminology.

12. (Amended) A [~~multispecific~~] bispecific antibody prepared by the method comprising:

(a) expressing in a host cell a first polypeptide comprising a first heavy chain variable domain, a first or second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) expressing in the host cell a second polypeptide comprising a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) allowing the first and second polypeptides to dimerize by interaction of the first and second multimerization domains to form a [~~multispecific~~] bispecific antibody; and

(d) recovering the [~~multispecific~~] bispecific antibody from the host cell.

13. (Amended) A [~~multispecific~~] bispecific antibody comprising a first polypeptide and

second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) the second polypeptide which comprises a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) the first and second polypeptides dimerize by interaction of the first and second multimerization domains to form a [~~multispecific~~] bispecific antibody.

14. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the nucleic acid encoding the first polypeptide or the nucleic acid encoding the [~~additional~~] second polypeptide, or both, has been altered from the original nucleic acid to encode the multimerization domain or a portion thereof.

16. (Amended) The [~~multispecific~~] bispecific antibody of claim 14, wherein the multimerization domains of the first and [~~an additional~~] second polypeptide [~~comprise a protuberance and cavity, respectively~~] interact at an amino acid side chain protuberance of one of the first and second polypeptides and an amino acid side chain cavity of the other polypeptide.

17. (Amended) The [~~multispecific~~] bispecific antibody of claim 16 wherein at least one of the protuberance and cavity [~~are~~] is generated by [alterations] an alteration in which a

18. (Amended) A composition comprising the [~~multispecific~~] bispecific antibody of claim 13 and a carrier.

31. (Amended) The [~~multispecific~~] bispecific antibody of claim 13 wherein the antibody is anti-Ob-R/anti-HER3.

33. (Amended) The composition according to claim 18, wherein the [~~multispecific~~] bispecific antibody is anti-Ob-R/anti-HER3.

34. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 90% amino acid sequence identity.

35. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 95% amino acid sequence identity.

36. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 98% amino acid sequence identity.

37. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 99% amino acid sequence identity.

38. (Amended) The [~~multispecific~~] bispecific antibody of claim 13, wherein the first and second light chain variable domains have identical amino acid sequences.

Clean Set of All Pending Claims

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12. (Amended) A bispecific antibody prepared by the method comprising:

(a) expressing in a host cell a first polypeptide comprising a first heavy chain variable domain, a first or second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein a first binding domain is formed by the first heavy chain variable domain and the first or second light chain variable domain;

(b) expressing in the host cell a second polypeptide comprising a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) allowing the first and second polypeptides to dimerize by interaction of the first and second multimerization domains to form a bispecific antibody; and

(d) recovering the bispecific antibody from the host cell.

13. (Amended) A bispecific antibody comprising a first polypeptide and a second polypeptide, the bispecific antibody comprising:

(a) the first polypeptide which comprises a first heavy chain variable domain, a first or second light chain variable domain, and a first multimerization domain, wherein the first and second light chain variable domains have at least 80% amino acid sequence identity, and wherein

(b) the second polypeptide which comprises a second heavy chain variable domain, the first or the second light chain variable domain, and a second multimerization domain, wherein a second binding domain is formed by the second heavy chain variable domain and the first or second light chain variable domain, and wherein the first and second binding domains bind different antigens;

(c) the first and second polypeptides dimerize by interaction of the first and second multimerization domains to form a bispecific antibody.

14. (Amended) The bispecific antibody of claim 13, wherein the nucleic acid encoding the first polypeptide or the nucleic acid encoding the second polypeptide, or both, has been altered from the original nucleic acid to encode the multimerization domain or a portion thereof.

16. (Amended) The bispecific antibody of claim 14, wherein the multimerization domains of the first and second polypeptide interact at an amino acid side chain protuberance of one of the first and second polypeptides and an amino acid side chain cavity of the other polypeptide.

17. (Amended) The bispecific antibody of claim 16 wherein at least one of the protuberance and cavity is generated by an alteration in which a naturally occurring amino acid is imported into the first or second polypeptide.

18. (Amended) A composition comprising the bispecific antibody of claim 13 and a carrier.

33. (Amended) The composition according to claim 18, wherein the bispecific antibody is anti-Ob-R/anti-HER3.

34. (Amended) The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 90% amino acid sequence identity.

35. (Amended) The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 95% amino acid sequence identity.

36. (Amended) The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 98% amino acid sequence identity.

37. (Amended) The bispecific antibody of claim 13, wherein the first and second light chain variable domains have at least 99% amino acid sequence identity.

38. (Amended) The bispecific antibody of claim 13, wherein the first and second light chain variable domains have identical amino acid sequences.